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Endolymphatic sac tumors in von Hippel–Lindau disease

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Object. Von Hippel–Lindau (VHL) disease is a hereditary multiple-neoplasia syndrome mapping to chromosome 3p25–26. Endolymphatic sac (ELS) tumors have been identified as a neoplastic manifestation of VHL disease. The purpose of this study was to evaluate comprehensively the natural history of inner ear disease in a large population of patients with confirmed or suspected VHL disease and to correlate the clinical features with the VHL genotype.

Methods. The authors collated and analyzed clinical and genotypic data obtained in patients enrolled in an Institutional Review Board–approved protocol in which families and individuals affected by VHL disease were studied. These data included results from multidisciplinary history workups and physical examinations, imaging studies, and a battery of audiological tests.

One hundred seventy-five patients were enrolled in the study, 129 with confirmed VHL disease and 46 of their family members in whom test results for VHL disease were negative and who served as controls. Twenty-one patients had ELS tumors that were evident on magnetic resonance images; three of them had bilateral ELS lesions. Hearing loss, often sudden in onset and severe to profound in nature, vestibulopathy, aural fullness, and tinnitus represented the primary symptoms of ELS tumor. Distinct patterns of auditory and vestibular dysfunction occurred at different stages of the disease. Phenotypic data showed that 17 of 21 patients with ELS tumors did not have pheochromocytomas, whereas all had VHL disease affecting the kidney, all but two had VHL disease affecting the central nervous system, and all but one had disease affecting the pancreas. Genotyping revealed 10 rearrangements (partial deletions), eight single bp substitutions, and one 3-bp insertion. Although there was no difference in the incidence of hearing loss between populations, symptoms of imbalance and aural fullness were more common in patients with VHL disease but without imaging evidence of ELS tumor than they were in family members who did not have VHL disease ($p < 0.01$).

Conclusions. Endolymphatic sac tumors are frequently associated with VHL disease. Symptoms of disequilibrium or aural fullness in patients with VHL disease may be an early indication of endolymphatic dysfunction. Patients with VHL disease provide a unique opportunity to examine the effects of specific gene mutations and a discrete neoplastic process on the human inner ear. The study of ELS tumors in this group also provides a pathological model of ELS function and supplies evidence for a role of the ELS in clinical Ménière-like disease(s).

KEY WORDS • von Hippel–Lindau disease • endolymphatic sac • Ménière disease • adenocarcinoma • inner ear

INDIVIDUALS affected by VHL disease (OMIM [Online Mendelian Inheritance in Man] 193300) are predisposed to the development of hemangioblastomas of the CNS, retinal hemangioblastomas, renal cysts, and carcinomas, pheochromocytomas, pancreatic cysts, and epididymal cystadenomas.[4,10] The diagnosis of VHL disease is further subclassified into Type 1 and Type 2 disease based on the absence (Type 1) or presence (Type 2) of pheochromocytoma.[3,4,6] Recently, the *VHL* gene product has been identified in basic studies as a protein (pVHL) that regulates proteosomal degradation of a number of proteins, including a prime target of VHL protein, hypoxia inducible factor 1.[23]

Primary low-grade adenocarcinomas (also called aggressive papillary cystadenomas) of the ELS recently have been clinically identified as another neoplastic manifestation of VHL disease.[11,12,20,21] The clinical connection of ELS tumor to VHL disease has since been confirmed using molecular techniques, which demonstrated loss of heterozygosity at the VHL locus in tumor cells from resected ELS tumors.[20–22]

We sought to determine the natural history of audiovestibular dysfunction with ELS tumors, to identify potential genotype–phenotype correlations within the subset of the population with VHL disease and ELS tumor to determine whether a distinct "hearing loss without ELS tumor" phenotype occurs, and to examine certain features of ELS tumors with respect to theories of the origins of Ménière disease.

Abbreviations used in this paper: ABR = auditory brainstem response; CNS = central nervous system; CPA = cerebellopontine angle; CT = computerized tomography; ELS = endolymphatic sac; IAC = internal auditory canal; MR = magnetic resonance; PTA = pure tone average; VHL = von Hippel–Lindau.

Clinical Material and Methods

Patient Population

One hundred seventy-five patients were enrolled in this study; 129 of them had confirmed VHL disease and 46 were members of families in which VHL disease had been diagnosed but who tested negative for VHL disease on genotyping and clinical screening. Twenty-one patients had ELS tumors that were evident on MR imaging and/or CT scanning; three of these 21 patients had bilateral ELS tumors. Female outnumbered male patients 13:8; the mean age at the time of evaluation was 37.4 years (range 11–77 years).

Enrollment and Evaluation

All participants were enrolled in a multidisciplinary protocol (89-C-0086) in which the authors prospectively examined individuals or families with confirmed VHL disease or who were at risk for VHL disease based on their family history of clinical manifestations. The screening protocol included evaluations by an audiologist, medical geneticist, urological oncologist, ophthalmologist, neurosurgeon, and neuro-otologist. Laboratory studies included standard serum chemistry, complete blood counts, thyroid panels, and urinalysis as well as 24-hour urine screening for catecholamines. Routine neuroimaging studies included Gd-enhanced MR imaging of the brain and spinal cord and contrast-enhanced CT scanning of the abdomen and pelvis. Patients were classified as with or without VHL disease based on the results of genetic and clinical testing. When indicated by auditory or vestibular symptoms, Gd-MR and CT studies of the IACs and the region of the ELS were performed. A comprehensive audiological assessment that included pure tone thresholds, speech audiometry, acoustic immittance testing, ABRs, and both distortion product and transient evoked otoacoustic emissions were performed in all individuals included in this study.

Exclusion Criteria for Audiological Analysis

All patients included in the audiological statistical analysis met the following criteria: 1) normal middle ear function as defined by admittance tympanometric peaks at 50 daPa or less and air/bone gaps at 10 dB or less; and 2) no history of significant noise exposure (that is, from regular or long-standing occupational or recreational sources), whole-brain radiation therapy, chemotherapy, sudden postsurgical hearing loss or sudden hearing loss of known origin, closed head trauma with loss of consciousness, nonsyndromic familial hearing loss, or hearing loss of known origin other than VHL disease (Table 1).

Statistical Analysis of Audiological Test Results

Audiological test results were collected from each ear of each participant. For a review of standard audiometric techniques, see Yellin.[24] All instruments met applicable calibration standards in double-walled sound suites that met American National Standards Institute criteria.[1] Three groups were initially analyzed: patients with VHL disease with and without ELS tumor(s), and individuals testing negative (by clinical and genotyping) for VHL disease. (This last group represented a control population that was composed of unaffected family members of patients with VHL disease.)

TABLE 1

*Criteria for exclusion from statistical audiological analysis**

Exclusion Category	Patients W/ VHL Disease	Patients W/O VHL Disease	Total No. of Patients
noise exposure	13	8	21
middle ear disease	5	2	7
postop hearing loss	5	0	5
head trauma	3	2	5
whole-brain radiation therapy	4	0	4
nonsyndromic familial hearing loss	0	4	4
other	1	1	2
non-VHL inner ear disease	0	1	1

* Patients may have been excluded from statistical analysis for more than one reason.

The pure tone threshold data were analyzed for each ear at 0.5, 1, 2, 4, and 6 kHz. Although 8-kHz thresholds were obtained, the nonnormal distribution of thresholds at those frequencies precluded a meaningful statistical analysis. A maximum threshold of a 110-dB hearing level was used when participants had no response. Speech recognition thresholds and word recognition scores for each ear were also compared among the different groups. For ABRs, absolute latencies of waves 1, 3, and 5, and interpeak latencies 1 to 3 and 1 to 5 were compared for each ear among the different control groups. To control for normal age-related changes, the group with VHL disease who did not have ELS tumors was compared with age- and sex-matched control patients tested in our clinic by the same audiologists. Given the number of patients with VHL disease who did not have ELS tumors, patients were grouped according to age (20–29, 30–39, 40–49, and 50–59 years of age) and these groups were then compared with similar historical control patients. Audiological data were transferred from a spreadsheet to an SAS software system (SAS Institute, Inc., Cary, NC) for statistical analysis. A Kruskal–Wallis rank-sum test was used to compare pure tone thresholds (at each frequency tested) for each ear, between each group. A similar analysis was applied for speech audiometric scores, ABR, and otoacoustic emission data. For the age- and sex-matched comparisons, a paired t-test was used to analyze pure tone and speech audiometry scores.

Results

Clinical Phenotypic and Genotypic Features of Patients With VHL Disease and ELS Tumors

Table 2 shows the phenotypic and genotypic characteristics of the 21 patients with VHL disease in whom ELS tumor was demonstrated on neuroimaging. Most patients (17 of 21) had a severe VHL phenotype, including benign and malignant neoplasms and cysts of the kidney, CNS, eye, and pancreas. Four of 17 patients had adrenal pheochromocytomas, which placed them in a Type 2 VHL disease group. Other manifestations of VHL disease are also shown in Table 2.

Analysis of genotypic data from these 21 patients showed a spectrum of mutations. A large proportion (10 of 21) showed rearrangements, that is, partial deletions, within the VHL encoding region. Nevertheless, because six of these 10 individuals were from just two families, it was not pos-

TABLE 2

*Clinical phenotypes and genotypes in individuals with ELS tumors**

Case No.	Age (yrs), Sex	Ear	Phenotype						Genotype†
			CNS	Ret	Kid	Pan	Adr	Ep	
1	27, M	both	X	X	X	X		X	rearrange
2	41, F	both			X	X			514 C>G
3	35, M	both	X	X	X	X	X	X	rearrange‡
4	44, F	rt	X	X	X	X			rearrange‡
5	40, M	rt	X	X	X	X			rearrange‡
6	59, F	rt	X	X	X	X			rearrange§
7	28, F	rt	X	X	X	X			rearrange§
8	31, M	rt	X	X	X	X	X		699 C>G
9	36, F	rt	X	X	X	X			rearrange
10	40, M	rt	X	X	X	X			430 C>T
11	27, F	rt		X	X	X			rearrange
12	21, F	lt	X		X	X			470 C>G
13	46, M	lt	X		X				712 G>A
14	46, M	lt	X	X	X	X			553 G>C
15	50, M	lt	X	X	X	X	X	X	ND
16	54, F	lt	X	X	X	X			674 C>T
17	32, F	lt	X	X	X	X			3-bp insertion, SA site
18	35, F	lt	X	X	X	X			769 G>T
19	54, F	lt	X	X	X	X			rearrange
20	53, F	lt	X	X	X	X			ND
21	45, F	lt	X	X	X	X	X		rearrange§

* Adr = adrenal pheochromocytoma; ep = epididymis; kid = kidney; ND = not done; pan = pancreas; rearrange = genetic rearrangement; ret = retina; SA = splice acceptor.

† Numbers indicate bp position with the sequencing-identified mutation.

‡ Individuals from one family.

§ Individuals from another family.

sible to generalize the interpretation of these data. Eight patients showed point mutations (single bp substitutions), which were distributed in each of the three exons of the *VHL* gene. One case of a 3-bp insertion at a splice acceptor site was identified.

Neuro-Otological Manifestations of ELS Tumors

Twenty of 21 patients with an ELS tumor visible on MR images reported subjective hearing loss (Table 3). In view of the frequent presentation of these patients late in the course of their disease, patients who reported decreased hearing ability were asked if they had experienced hearing loss within the past year, for less than 5 years, less than 10 years, or more than 10 years. Ten patients recalled a hearing loss of more than 10 years' duration, suggesting a long-standing existence of their ELS tumor (Table 4). Overall, nine patients (43% of patients; 38% of affected ears) reported a sudden hearing loss (typically noted on waking or while listening to a conversation or watching television), nine patients (43%) described progressive hearing loss noticed over the course of 3 to 6 months, and the remaining three patients (14%) recalled a more insidious or gradual hearing loss.

TABLE 3

Neuro-Otological symptoms in 21 patients with ELS tumors visible on MR imaging

Symptom	No. Affected
hearing loss	20
tinnitus	17
vertigo	14
disequilibrium	5
aural fullness	5
other	1

Patients with ELS tumors also frequently reported tinnitus; 17 of these 21 patients complained of significant tinnitus. Specifically, patients were asked if they experienced noises in their ear(s) or head that were "bothersome" (interfering with hearing, sleep, or concentration, and so forth) and lasting for several hours or more. Approximately half of the group (eight patients) reported a low-pitched "roaring" or "rushing" quality to the tinnitus, whereas others described a high-pitched ringing or tone-type sound. Five (29%) of 17 reported bilateral tinnitus (two of these five patients had bilateral tumors), eight (47%) of 17 had unilateral tinnitus corresponding to the ear affected by the ELS tumor, one (6%) of 17 had unilateral tinnitus in the ear not affected by the ELS tumor, and four patients (23%) could not localize their tinnitus to either or both ears. Six patients (35%) had previously sought medical attention specifically for their tinnitus. A large proportion of the patients with VHL disease who did not have an ELS tumor also reported hearing loss and tinnitus (Table 5).

A common feature among individuals with long-standing ELS tumors is a history of vertiginous episodes that subside with time. A typical history of peaking vestibular symptoms around the time of hearing loss was also noted (10 of 14 patients with an ELS tumor and symptoms of vertigo reported such a history). In view of the frequent simultaneous occurrence of cerebellar and brainstem hemangioblastomas in patients with VHL disease, careful analysis of

TABLE 4

Patterns of hearing loss in patients with ELS tumors visible on MR imaging

Case No.	Side W/ ELS Tumor	Hearing Loss		
		Onset	Duration	Pattern
1	bilat	side 1: sudden side 2: insidious	<5 yrs*	side 1: profound side 2: mild, mid-frequencies
2	bilat	side 1: progressive side 2: insidious	<10 yrs*	side 1: mod severe, flat side 2: mild, high frequencies
3	bilat	side 1: sudden side 2: insidious	<1 yr*	side 1: mod, low frequencies side 2: mild, high frequencies
4	rt	progressive	>10 yrs	profound
5	rt	sudden	>10 yrs	profound
6	rt	progressive	>10 yrs	mod severe, flat
7	rt	sudden	>10 yrs	profound
8	rt	sudden	<5 yrs	mod severe, flat
9	rt	progressive	<10 yrs	mod severe, flat
10	rt	sudden	>10 yrs	profound
11	rt	sudden	>10 yrs	profound
12	lt	progressive	<1 yr	low frequencies
13	lt	sudden	>10 yrs	mod severe, flat
14	lt	progressive	>10 yrs	profound
15	lt	progressive	>10 yrs	profound
16	lt	insidious	<1 yr	low frequencies
17	lt	sudden	>10 yrs	profound
18	lt	progressive	<5 yrs	mod severe, flat
19	lt	progressive	<10 yrs	profound
20	lt	insidious	<10 yrs	mod severe, flat
21	lt	insidious	<1 yr†	high frequencies

* Duration for the ear with sudden or progressive hearing loss.
† Hearing loss not noted by the patient but demonstrated by serial audiometry.

patient data was needed to distinguish between a central cause of balance disturbance and true peripheral vestibular disease. Five (29%) of 17 patients had symptoms, imaging findings, and/or vestibular test results consistent with a cerebellar or brainstem origin rather than inner ear dysfunction. Five patients (29%) described ear pressure or fullness of long-standing duration in the ear affected by the ELS tumor. In all of these patients tympanic membranes were normal on microscopic examination, there was no evidence of middle ear disease, and all patients showed normal middle ear function on immittance testing. One patient reported frank ear pain on the side with an ELS tumor, for which no other cause could be identified.

Neuro-Otological Function in the Screened Population

Table 5 presents the demographic data and subjective symptoms in the overall screened population (patients both with and without VHL disease). There was no difference in the incidence of subjective hearing loss or tinnitus between the group with VHL disease but without ELS tumors and the group without VHL disease. A 48% and 46% incidence of subjective tinnitus in the groups with and without VHL disease, respectively, was surprisingly high. A purposefully open-ended inquiry made when the patient's history was being obtained (that is, "Have you ever experienced noises in your ears or head?") may account for a large number of positive responses. Factors such as recreational and occupational noise exposure noted for many of these patients may account for another large proportion of individuals with tinnitus (particularly among men).

Audiological Results in Patients With ELS Tumors and in a Large-Scale Screening of Individuals At Risk for VHL Disease

A summary of the pure tone and speech audiometry test results from patients with a radiologically evident ELS tumor is shown in Table 6. Although these data show the obvious difference in mean scores between ears with an ELS tumor visible on MR imaging and those without, the distribution of hearing levels is highlighted in Fig. 1, which shows a scatterplot of the four-tone PTAs (calculated by averaging the thresholds at 0.5, 1, 2, and 4 kHz). Note that the ears without ELS tumor show a clustering above the normal 20-dB hearing level. The poorest PTA among ears without ELS tumors was a 5-dB hearing level. In contrast, the PTAs for ears affected by ELS tumors show a wide variation, with several patients recording PTAs at the highest limits of testing. The variation in this subgroup of ears reflects the various stages of ELS disease at which patients were tested.

An obvious difference in pure tone thresholds between patients with ELS tumors and all other groups was evident ($p < 0.0001$, Kruskal–Wallis test). Similarly, speech reception threshold and speech recognition scores were significantly different from all other groups ($p < 0.01$). The ABR latencies of the group with ELS tumors were not statistically significantly different ($p < 0.065$, data not shown) when compared with the group with VHL disease but without

TABLE 5

Demographic data and symptomatology in the overall screened population

Group	No.	Age (yrs)			Symptom (%)				
		Mean	Median	Range	Hearing Loss	Tinnitus	Vertigo	Disequilibrium	Aural Fullness
F w/ VHL*	61	35.6	36	13–69	22 (36)	25 (41)	10 (16)	26 (43)	9 (9)
M w/ VHL*	47	36.2	38	11–77	19 (40)	27 (57)	6 (13)	17 (36)	9 (19)
subtotal	108				41 (38)	52 (48)	16 (15)	43 (40)†	18 (17)†
F w/o VHL	25	36.8	36	11–77	8 (32)	13 (52)	2 (8)	5 (24)	2 (10)
M w/o VHL	21	39.9	36	17–69	8 (38)	8 (38)	2 (10)	3 (14)	1 (5)
subtotal	46				16 (35)	21 (46)	4 (9)	8 (17)	3 (7)

* Does not include 21 patients with VHL disease in whom ELS tumor(s) were observed on MR or CT studies.
† $p < 0.01$ compared with patients without VHL disease, chi-square test.

TABLE 6
*Audiological test results in patients with ELS tumors visible on MR imaging**

		Mean Values						
				Pure Tone Threshold (dB)				
Ear	No.	SRT (dB)	SR%	0.5-kHz	1-kHz	2-kHz	4-kHz	6-kHz
w/ tumor	24	66	38	70	68	66	74	74
w/o tumor	18	8	98	10	8	11	25	36

* SR% = speech recognition score; SRT = speech reception threshold.

ELS tumor or the group without VHL disease. Nevertheless, this is likely due to the exclusion of eight participants with ELS tumor in whom no ABR data were obtainable due to profound hearing loss and lack of measurable waveforms.

Neuro-Otological Function and Symptoms in Patients With VHL Disease Without ELS Tumors

Frequent reports of hearing loss in the group with VHL disease but without evidence of ELS tumors on neuroimaging led us to hypothesize that VHL mutations alone (that is, in the absence of MR imaging–confirmed ELS tumor) or lesions that are too small to be detected with MR imaging could cause sensorineural hearing loss or other symptoms associated with VHL disease. A comparison of audiological test results in patients with VHL disease in whom no ELS tumor was visible on MR imaging with test results in those who tested negative for VHL disease failed to show significant difference for any of the audiological test parameters measured (smallest p value > 0.1, Fig. 2). Similarly, the audiological test results in patients with VHL disease but no ELS tumor were compared with the test results from historical age- and sex-matched control patients who were tested under similar conditions. Again, no significant differences could be demonstrated between the two groups for any of the audiological parameters measured ($\alpha < 99.5\%$ by paired t-test, data not shown). Our results, therefore, did not support the hypothesis that VHL mutations alone, without ELS tumor involvement, produce a hearing loss phenotype.

In contrast to the audiological test results, there were significant differences in the incidence of symptoms of disequilibrium and aural fullness between the patients with VHL disease in whom there was no imaging evidence of an ELS tumor and the patients without VHL disease (both $p < 0.01$, chi-square test; Table 5). There was a trend toward a difference in the incidence of complaints of vertigo between these two groups, but it was not statistically significant ($p = 0.3$, chi-square test; Table 5).

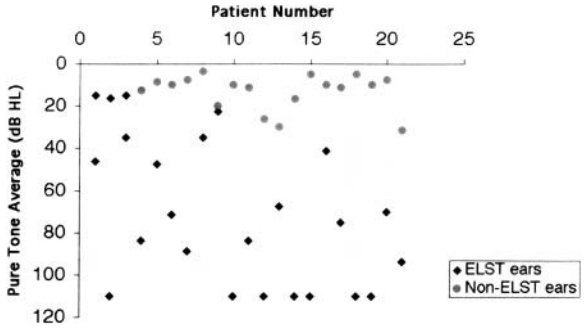

FIG. 1. Scatterplot of PTAs in 21 patients with ELS tumors (ELSTs). The four-tone PTA was calculated by averaging the pure tone threshold of each ear at 0.5, 1, 2, and 4 kHz in 21 patients with ELS tumors. Note that the ears without ELS tumors are clustered at the top end of the chart, primarily in the normal hearing range. In contrast, the ears with ELS tumors demonstrate a wide range of hearing levels as shown by their PTAs. Three ears with ELS tumors showed a normal PTA (that is, < 20-dB hearing level [HL]), whereas the remaining ears with ELS tumors all showed varying degrees of hearing loss (PTA between 25- and 110-dB hearing level).

Discussion

Natural History of Hearing and Balance Disturbances Due to ELS Tumors

The onset of hearing loss in patients with an ELS tumor remains an incompletely defined and troublesome issue. In this series, 43% of patients with an ELS tumor visible on MR imaging reported a sudden onset of deafness. Because serial imaging and audiological studies are not available for many of the patients immediately before and after their hearing loss, it is not possible to document precisely the sequence of events linking tumorigenesis and hearing symptomatology. As noted by Manski, et al.,[11] however, a trend is apparent between the duration of symptoms attributed to the ELS tumor and the degree of hearing loss. Based on our data, a large proportion of patients with VHL disease who experienced hearing loss (43% in our series) suffer sudden and presumably irreversible hearing loss. Our early experience with resection of ELS tumors indicates that hearing can often be preserved but not restored by resection. By comparison, 43% of our patients with ELS tumors experienced progressive hearing loss. These patients represent a group for whom intervention at the earliest onset of aural symptoms might stabilize hearing at useful levels before the disease progresses. At this point, patient history and imaging studies (high-resolution Gd-enhanced MR imaging and CT scanning of the IACs) provide the highest sensitivity for diagnosing early ELS tumors. Our continuing prospective study (using audiological and imaging methods) of patients with VHL disease who are at risk for ELS tumor should help to determine the association of hearing loss with tumorigenesis, and permit development of diagnostic and therapeutic strategies based on knowledge of the natural history of the disease.

With the use of a routine screening program for patients affected by VHL disease (clinical examination, audiologi-

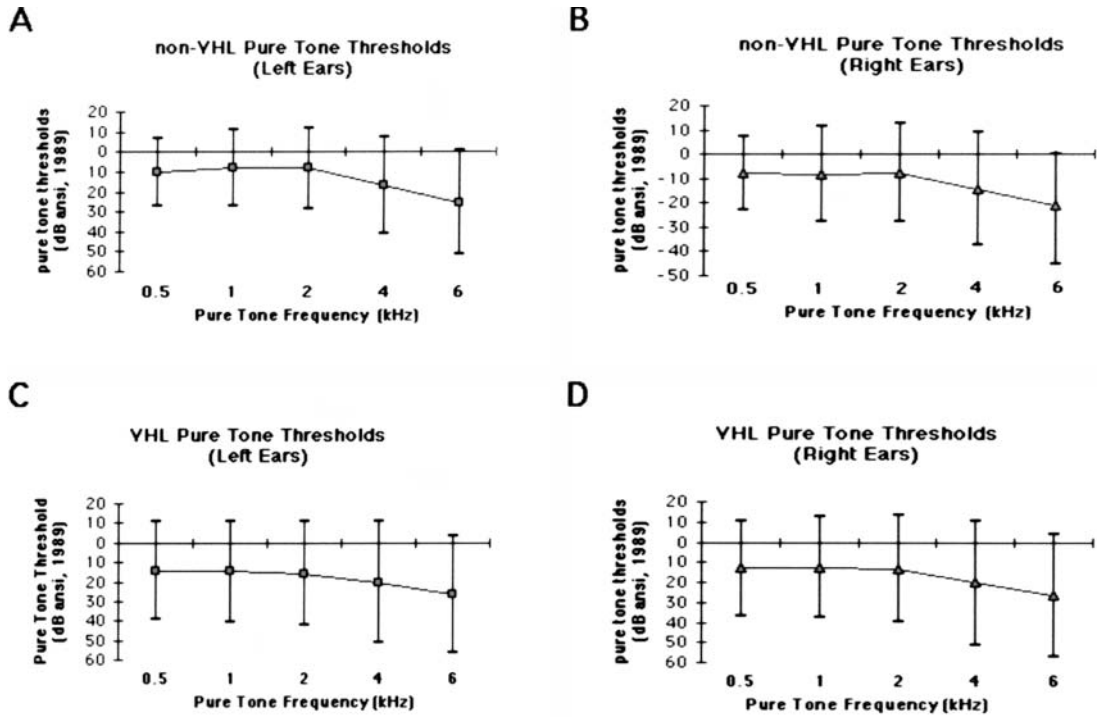

FIG. 2. Graphs showing pure tone thresholds in patients with VHL disease without ELS tumor and in patients without VHL disease. The data were collated and analyzed to determine if patients with VHL disease in whom there was no imaging evidence of ELS tumor demonstrated hearing loss. The mean pure tone thresholds for the right and left ears of patients with VHL disease but without imaging evidence of ELS tumor (labeled VHL) and those unaffected by VHL disease (labeled non-VHL) are shown. Pure tone threshold data were obtained in each patient at octave intervals between 0.5 and 6 kHz. The mean values for each group are represented by *squares* or *triangles*, with error bars indicating one standard deviation above and below the mean. No statistically significant difference was identified between any of the groups. These data indicate that VHL disease alone, in the absence of an ELS tumor on MR images, is not associated with hearing loss and that hearing loss in patients with VHL disease indicates the presence of an inner ear tumor. Ansi = American National Standards Institute.

cal testing, and focused imaging studies), we identified four patients with what appeared to be early-stage ELS tumors. In this limited group, an isolated low-frequency hearing loss seems to be a fairly common feature (three of four patients). All four patients described the onset of hearing changes within 6 to 8 months of presentation. Pathological studies confirmed a small tumor confined to the ELS in a patient who presented with a 6-week history of sudden low-frequency hearing loss and mild vertigo and who elected to undergo resection of her lesion (Figs. 3 and 4).

A second subset of patients with a severe sensorineural hearing loss of approximately 60 to 70 dB represents individuals with intermediate-stage disease. Note that five of seven patients with this type of hearing loss reported that its duration was between 5 and 10 years. Finally, in patients who have had ELS tumors for more than 10 years, hearing loss progresses to profound levels, presumably due to direct erosion of the tumor into the inner ear structures. Eight of 10 patients with profound hearing loss reported that its duration was more than 10 years. The results of the imaging studies obtained in patients with large and presumably late-stage ELS tumors provide anatomical evidence to support this mechanism.

Vestibulopathy with ELS tumors appears to follow a pattern of severe symptomatology with subsequent milder or asymptomatic periods. Most vestibular symptoms seem to peak around the time of active hearing loss; patients with ELS tumors describe severe symptoms lasting 6 to 12 months, after which they gradually abate. This pattern is consistent with unilateral vestibulopathy, which either "burns out" or for which there is central compensation, as seen in other unilateral inner ear diseases (for example, Ménière disease).

Association of ELS Tumors With Inner Ear Dysfunction

A vast body of literature indicates that the ELS plays a role in the pathogenesis of Ménière disease as well as its histopathological correlate, endolymphatic hydrops.[7,13–17] In animal studies, lesioning of the endolymphatic apparatus has provided pathological models of ELS function.[8] Patients with VHL disease who have ELS tumors provide a unique opportunity to study a pathological model of human ELS function. Our observations of patients with ELS tumors demonstrate a striking clinical similarity between individuals with these lesions and those affected by Ménière disease, and from this we infer that localized pathological conditions in the ELS can result in Ménière disease–like symptoms.

Other hypotheses on the effects of ELS tumors on inner ear function will likely stem from basic investigations into the function of the *VHL* gene product. In other organ systems and VHL tumors, loss of normal *VHL* gene function results in changes in local vascularity as well as epithelial

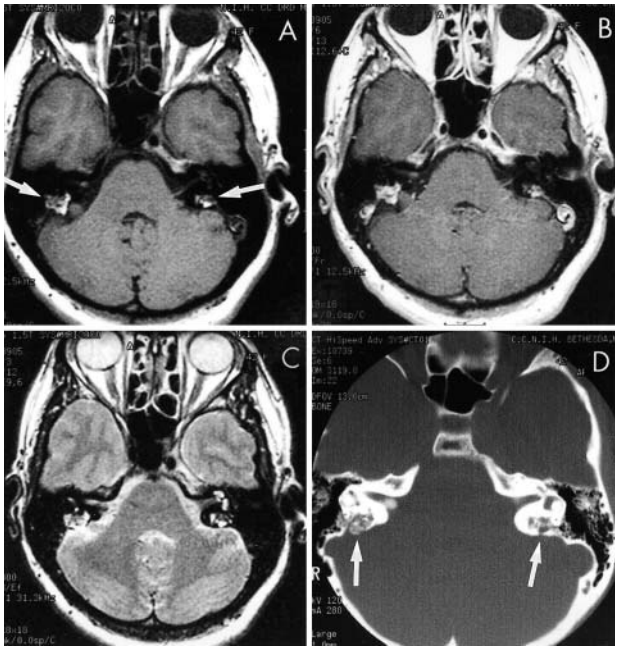

FIG. 3. Neuroimaging features of ELS tumors. Axial T_1-weighted pre- (A) and post-Gd (B) MR images obtained at the level of the IACs. *Arrows* in A indicate the bilateral ELS tumors in this patient who had bilateral hearing loss. C: Axial T_2-weighted MR image demonstrating the bilateral tumors. D: Axial high-resolution CT scan illustrating the typical bone erosion along the posterior petrous bone bilaterally *(arrows)* in the region where ELS tumors originate.

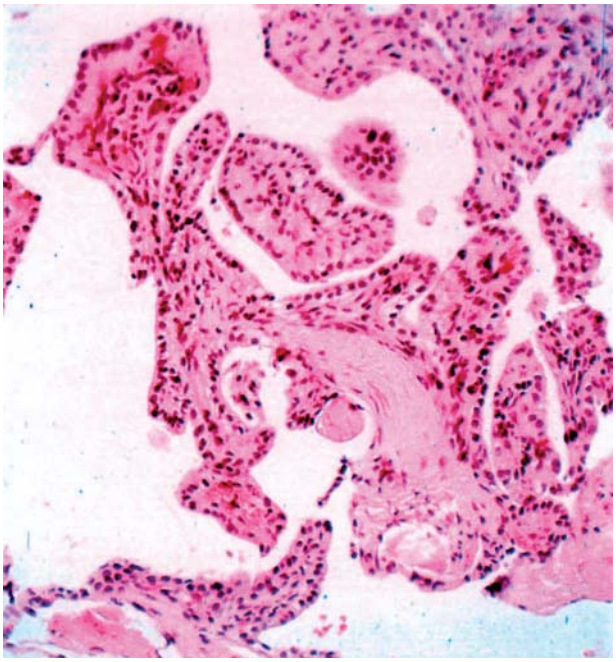

FIG. 4. Photomicrograph showing histopathological features of an ELS tumor; the typical papillary architecture is displayed. A simple cuboidal-type epithelium with a fibrous stroma is seen in these tumors; mitotic profiles are rare. The histopathological features of these lesions are relatively benign despite their locally aggressive growth and bone erosion. H & E, original magnification × 25.

permeability (likely through vascular endothelial growth factor/vascular permeability factor).[2,9,19] In the ELS, it has been suggested that changes in blood supply and/or epithelial permeability play a role in malfunction of the sac.[13] Nevertheless, a cellular mechanism for explaining these changes has been lacking. Investigations into the effects of vascular endothelial growth factor on ELS epithelium and blood supply may provide new perspectives for this hypothesis. Observations made during surgery supply some evidence in support of this notion. The normally pale and avascular posterior surface of the petrous bone has shown tremendous neovascularization in some cases of ELS tumor.

It also seems likely that some patients in whom ELS tumors exist at a very early stage, a stage too early to be detected on MR images or CT scans and too early to produce hearing impairment, experience symptoms that herald the presence of a tumor in the ELS.[10] This may at least partially underlie the higher incidence of symptoms of disequilibrium and aural fullness in the patients with VHL disease in whom no ELS tumor is visible on MR imaging, compared with the family members without VHL disease (Table 5). If this is so and if a means of establishing the diagnosis of ELS tumor at that early stage, before inner ear injury has occurred, is identified, hearing preservation may be achieved with early surgery of the ELS.

Excision of ELS Tumors: Combined Transmastoidal–Suboccipital Approach

The primary goals of surgical therapy for ELS tumors are as follows: 1) complete resection of the tumor; and 2) preservation of residual hearing in the affected ear. The keys to accomplishing these goals depend on obtaining wide exposure of the posterior petrous bone and CPA region while avoiding trauma to the inner ear labyrinth or the cochleovestibular nerves in the IAC. The anatomical proximity of the ELS (and ELS tumors) to the inner ear and eighth cranial nerve complex, as well as the tendency of ELS tumors to erode into adjacent regions, makes surgery to preserve hearing a challenging task. Our surgical experience with ELS tumors, and that of others, has demonstrated that a combined transmastoidal–suboccipital approach offers the advantages required for hearing preservation combined with complete ELS tumor removal.[11,12]

Briefly, drilling commences with a standard cortical mastoidectomy in which the mastoid cortex and central mastoid air cell tracts are exenterated, leaving thin bone coverings over the sigmoid sinus, the middle fossa, and the posterior ear canal. After identifying the prominence of the horizontal semicircular canal, the vertical portion of the facial nerve is identified to avoid facial paralysis. Using the horizontal semicircular canal as a landmark, the posterior semicircular canal is then delineated using a series of cutting and diamond burrs. With the posterior semicircular canal identified, drilling can then be safely performed immediately behind the posterior semicircular canal and in front of the sigmoid sinus to remove the bone overlying the posterior fossa dura and the embedded ELS/ELS tumor. With this exposure obtained, a standard retrosigmoidal–suboccipital craniectomy is performed, with a dural incision then made just posterior to and paralleling the sigmoid sinus from a

point near its junction with the jugular bulb inferiorly to its transition into the transverse sinus superiorly. With cerebrospinal fluid drainage and limited cerebellar retraction, a wide exposure of the posterior temporal bone and CPA is obtained. This combined exposure then permits the surgeon to resect the tumor and involved dura while avoiding damage to the inner ear structures that would the result in sensorineural hearing loss.

The transmastoidal approach provides the advantage of permitting identification of the posterior semicircular canal while the tumor is being resected. Of all the vulnerable structures of the inner ear, this one is situated closest to the endolymphatic duct and sac. Inadvertent drilling into the posterior semicircular canal results in permanent deafness in most instances, yet exposure and drilling immediately adjacent to the posterior semicircular canal is required to remove ELS tumors completely.

The wide posterior fossa exposure of the tumor provides a direct line of sight toward the portion of the posterior petrous bone from which these tumors seem to originate and provides greater access than would be possible through the mastoid compartment alone. Accordingly, excision of larger tumors can be accomplished through the suboccipital craniotomy. A wide surgical exposure that offers the ability to obtain hemostasis may be associated with less morbidity than when resorting to preoperative embolization or carotid artery bypass.[5,18] Finally, the suboccipital exposure of the eighth cranial nerve complex in the CPA region provides the opportunity to perform continuous intraoperative ABR monitoring to enhance the success of preserving residual hearing. By placement of a direct cochlear nerve recording electrode on the eighth cranial nerve complex in the CPA region, the patient's hearing can be continuously monitored during tumor resection.

The combined transmastoidal–suboccipital approach provides the advantages of wide exposure, preservation of key inner ear structures, and intraoperative auditory monitoring that usually allow the surgeon to achieve the goals of complete resection with hearing preservation.

Conclusions

This study of a large population with VHL disease and a subset of patients with ELS tumor has provided a unique opportunity to correlate the clinical expression and imaging features of ELS tumors and to examine the role of the ELS in the inner ear. The information obtained also supports the importance of the ELS in other pathological conditions of the inner ear such as Ménière disease.

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